Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk

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Previous studies suggested that membranoproliferative glomerulonephritis (MPGN) type II has a worse renal survival and an unacceptable risk of recurrence post transplantation. We hypothesised that other factors may determine this risk. We analysed all cases ($n=70$) of MPGN diagnosed by renal biopsy in Ireland from 1972 to 1995. We used Cox regression analysis to determine factors that were independently predictive of renal failure. MPGN II had more crescent formation and mesangial proliferation ($P<0.05$). Mean follow-up duration was 13.8 years, during which time 41 (58.6%) developed end-stage renal failure (ESRF). The median time to ESRF was 8.3 years (95% confidence interval 5.7–10.9) and 5-, 10-, and 20-year probabilities of ESRF were 32, 54, and 70%, respectively. Multivariate analysis revealed that severity of interstitial fibrosis ($P<0.05$), crescent formation ($P<0.01$) and mesangial proliferation ($P<0.05$) were independently associated with ESRF. Decade of diagnosis, age, MPGN type, and creatinine or complement level at baseline did not predict renal survival in this model. In 21 (49%) of the 43 renal transplants, MPGN recurred. Younger age at initial diagnosis ($P<0.01$) and the presence of crescents on the original biopsy ($P<0.005$) were independently associated with recurrence on multivariate analysis. MPGN type was not associated with recurrence in this model. Contrary to previous reports, after controlling for crescent formation, MPGN II was not associated with more ESRF or recurrence in the allograft. It is therefore the more aggressive glomerular changes associated with MPGN II, rather than the disease type *per se*, that determine outcome.

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Membranoproliferative glomerulonephritis (MPGN) is an uncommon cause of chronic glomerulonephritis in the developed world.[1–3] It typically affects children and young adults with a mean age at onset ranging from 8 to 30 years.[4] MPGN is a disease that lacks any unique serological markers and has no pathognomonic clinical features, but rather is a histologically defined entity characterised by global and diffuse mesangial cell proliferation with migration of mesangium into the glomerular capillary walls, producing an apparent split or double-contoured appearance. It is seen in association with a variety of infections and other systemic diseases. In particular, it has become apparent that, in many parts of the world, hepatitis C virus (HCV), with or without associated cryoglobulinaemia, is an important aetiological factor for MPGN type I.[5,6] Several longitudinal outcome studies have been performed, most of which were published in the early 1990s. Of note, most of these studies were performed before the aetiological importance of HCV was appreciated. Therefore, we do not have accurate knowledge of the natural history in the idiopathic (non-HCV associated) form of this disease.

MPGN is classified into three subtypes on the basis of pathological features identified by light, immunofluorescence and electron microscopy. Type I MPGN is characterised by subendothelial deposits in the capillary wall. In type II MPGN, elongated electron dense densities are seen within the glomerular, tubular and Bowman's capsular basement membrane; hence, it is also referred to as 'linear dense deposit disease'. Previous studies have indicated a recurrence rate of 90% following renal transplantation for this type of MPGN.[7] Type III MPGN is a variant of type I in which there are many subepithelial as well as subendothelial deposits.[8,9]

Of note, we have previously reported that familial MPGN III may occur and is linked to a locus on chromosome 1,[8,9] an area that encompasses the regulators of complement cluster, suggesting a role for disordered complement regulation in the pathogenesis of this disease.

Because of the rarity of MPGN, guidance for physicians is based on case series performed mainly before 1990. The majority of these were published before the importance of HCV was known. In addition, factors potentially predictive of end-stage renal failure (ESRF) or recurrence of primary

disease in a transplant were frequently considered in isolation from each other. We were interested in what factors were independently predictive of outcome (ESRF and recurrence in the renal allograft) when analysed by multivariate analysis. Therefore, we performed a retrospective cohort analysis on a large group of patients with primary MPGN.

RESULTS

Histopathological characteristics at presentation

Of the 70 patients with primary idiopathic MPGN, 30 patients had type I disease (43%), 23 had type II (33%), and 17 had type III (24%). The percentages of cellular crescents, glomerular sclerosis, interstitial fibrosis and degree of mesangial proliferation are summarised in Figure 1. The light microscopic changes were very similar for types I and III. There was a significant increase in the percentage of fresh crescents ($P<0.05$) and degree of mesangial proliferation ($P<0.05$) in type II MPGN.

Clinical characteristics at presentation

The clinical characteristics at presentation are summarised in Table 1. Mean age was 24.9 years (range 3–76) and 41 (59%) were male. Type II patients were younger ($P=0.001$) and exhibited a female preponderance ($P<0.05$), which contrasts with a slight male preponderance among those with type I or III disease. All type III patients had nephrotic-range proteinuria at presentation compared to two-thirds of those with type I or II disease ($P<0.05$). There was no significant difference in the prevalence of hypocomplementaemia at presentation.

Renal survival

Univariate analysis. During the period of follow-up, 41 patients (58.6%) became dialysis dependent. Univariate analyses of factors associated with this outcome measure are summarised in Table 2. There were 11 deaths (16%) during the period of follow-up, all of which occurred after the development of ESRF. Figure 2 depicts the unadjusted probability of developing ESRF over time. The overall median time to ESRF from diagnosis was 8.3 years (95% confidence interval (CI) 4.4–12.3) and 5-, 10-, and 20-year probabilities of ESRF were 32, 54, and 70%, respectively. Using life table survival analysis, the presence of nephrotic-range proteinuria ($P<0.01$), cellular crescents on biopsy at diagnosis ($P<0.005$), degree of mesangial proliferation ($P<0.005$) and degree of interstitial fibrosis ($P<0.01$) were associated with a higher propensity to ESRF (Figure 3). Interestingly, neither MPGN type ($P=0.6$; Figure 3), treatment modality ($P=0.5$) nor complement profile at presentation ($P=0.9$) was associated with ESRF. There was no cohort effect, with the same probability of ESRF observed in the three cohorts ($P=0.3$). Renal survival probability was the same in patients with accurate treatment data ($n=59$) and those without ($n=11$, $P=0.5$).

We evaluated a predictive scoring system for two groups of patients. Firstly, in those patients with no cellular crescents, $<20\%$ interstitial fibrosis and $\leqslant +2$ mesangial proliferation ($n=16$), median renal survival was 13.8 years and 10-year probability of ESRF was 12%. This compared to a median renal survival of 6.4 years and 10-year ESRF probability of 69% in those without this triad ($n=54$; hazard ratio 0.21, 95% CI 0.15–0.70, $P<0.005$). Secondly, nephrotic patients with at least one cellular crescent ($n=18$) exhibited a median renal survival of 4.5 years and 10-year ESRF probability of 92%. This compared to a median renal survival of 11.9 years and 10-year ESRF probability of 41% in those without the combination of nephrotic syndrome and crescentic nephritis ($n=52$; hazard ratio 3.0, 95% CI 2.0–11.9, $P<0.0005$).

Multivariate analysis. Using multivariate Cox regression analysis, the degree of interstitial fibrosis ($P<0.05$), degree of mesangial proliferation ($P<0.05$) and the presence of at least one cellular crescent at diagnosis ($P<0.01$) were independently associated with ESRF (Table 3).

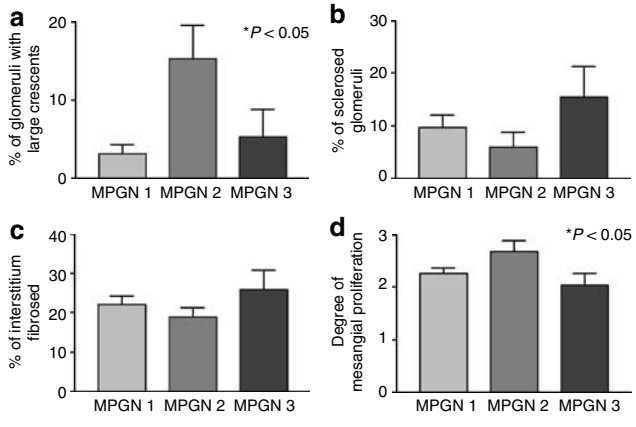

Figure 1 | Histopathological characteristics at diagnosis. (**a**) Mean cellular crescent fraction was 3.1 ± 1.2, 15.3 ± 4.3 and $5.3\pm3.5\%$ for types I, II and III, respectively. (**b**) Respective values for percentage of glomeruli sclerosed were 9.7 ± 2.4, 5.9 ± 2.9 and $15.4\pm5.9\%$, for percentage of interstitium fibrosed (**c**) 21.9 ± 2.3, 18.9 ± 2.1 and $25.7\pm5.0\%$ and for degree of mesangial proliferation (**d**) 2.3 ± 0.1, 2.7 ± 0.2 and 2.0 ± 0.2. The bars represent the mean $\pm$ s.e.m. *$P<0.05$.

Table 1 | Clinical characteristics of the patients at presentation according to MPGN type

	Type I	Type II	Type III	*P*-value
Age (years) (mean, range)	33.2 (5–76)	13.7 (4–34)	26 (3–66)	0.001
Male (*n*, %)	22 (73)	8 (34)	11 (64)	0.02
Creatinine (mg/dl) (median, IQR)	0.9 (0.6–1.9)	0.8 (0.6–1.3)	0.8 (0.7–1.4)	0.23
Nephrotic at presentation (*n*, %)[a]	18 (64)	15 (65)	15 (100)	0.03
Low C3 at presentation (*n*, %)[b]	12 (46)	5 (29)	7 (58)	0.28

IQR=interquartile range.
[a]*n*=66.
[b]*n*=55.

Table 2 | Univariate analysis of factors potentially associated with the development of ESRF

	ESRF	No ESRF	*P*-value
Age (years) (mean, s.d.)	24.1 (18.5)	26.1 (19.7)	0.4
Gender (n, %)			
Male	25 (61)	16 (39)	0.83
Female	16 (55)	13 (45)	
MPGN classification (n, %)			
I	16 (53)	14 (47)	0.59
II	15 (65)	8 (35)	
III	10 (59)	7 (41)	
Nephrotic at presentation (*n*, %)	32 (67)	5 (28)	0.009
Low C3 (n, %)			
Yes	18 (58)	13 (42)	0.91
No	13 (54)	11 (46)	
Cohort (n, %)			
1970s	14 (70)	6 (30)	0.27
1980s	16 (53)	14 (47)	
1990s	11 (55)	9 (45)	
Creatinine (mg/dl) (median, IQR)	0.9 (0.6–2.0)	0.9 (0.6–1.2)	0.06
Treatment modality (n, %)			
None	4 (44)	5 (56)	0.5
Steroid	5 (27)	15 (73)	
BP[a]	19 (64)	11 (36)	
Mesangial proliferation (mean, s.d.)	2.6 (0.9)	2.0 (0.6)	0.002
Interstitial fibrosis (%) (mean, s.d.)	25.2 (11.5)	17.7 (14.2)	0.008
Cellular crescents (%) (mean, s.d.)	12.1 (18.2)	1.7 (4.0)	0.003[b]

ESRF, end-stage renal failure; MPGN, membranoproliferative glomerulonephritis; IQR, interquartile range; BP, bloal pressure
The variables are compared with Kaplan–Meier life table analysis using the log-rank test.
[a]BP: antihypertensive therapy alone.
[b]Comparing those with crescents with those without crescents; IQR: interquartile range.

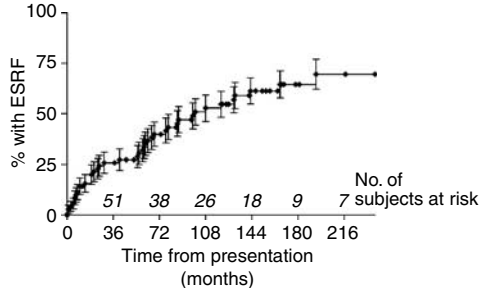

Figure 2 | Unadjusted Kaplan–Meier survival curve depicting likelihood of reaching ESRF. Overall median time to ESRF from diagnosis was 8.3 years (95% CI 4.4–12.3) and 5-, 10- and 20-year probabilities of ESRF were 32, 54 and 70%, respectively. Error bars depict the s.e.m.

Recurrence in the renal allograft

Univariate analysis. There were 43 renal transplants in 33 patients. In 21 (49%) of these, MPGN recurred after a median of 4.7 years. In all of these, the diagnosis was confirmed immuno-histologically and with electron microscopy. Of those who suffered a recurrence of MPGN in the graft, 14 (67%) ultimately lost their graft. The median time to graft failure was 7.5 years. Given that the data are censored for graft loss owing to patient death, this is likely to represent a reduction in graft half-life (a view supported by a recent report suggesting increased rates of graft loss in patients with recurrent MPGN type II).[10]

Considering the probability of recurrence over time using life table analysis, younger age at initial diagnosis ($P<0.05$), the degree of mesangial proliferation ($P<0.05$) and crescent formation on the original biopsy ($P<0.05$) were associated

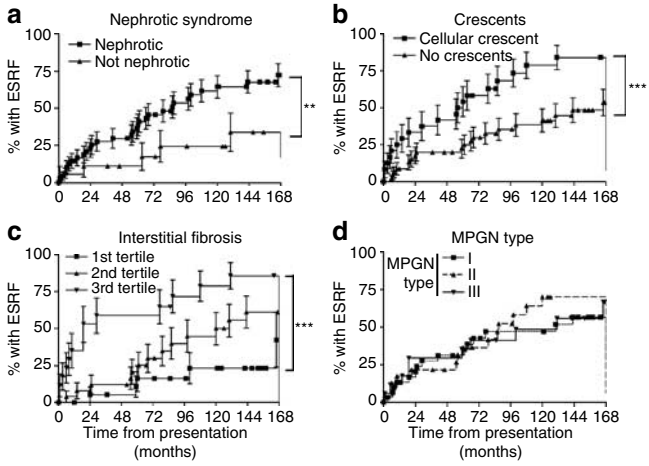

Figure 3 | Kaplan–Meier survival curves depicting the likelihood of reaching ESRF based on the following. (**a**) The presence or absence of nephrotic syndrome at diagnosis. The 5-year probability of ESRF was 37% in the presence of nephrotic syndrome (■) and 12% in its absence (▲, $^{**}P<0.01$). (**b**) The presence or absence of at least one cellular crescent at diagnosis. The 5-year probability of ESRF was 52.5% with one or more crescents (■) and 22.5% with no crescents (▲, $^{***}P<0.005$). (**c**) The tertiles of interstitial fibrosis. The 5-year probability of ESRF was 58% with >25% (▼), 21% with 10–25% (▲) and 8% with <10% interstitial fibrosis (■, $^{***}P<0.001$). (**d**) MPGN type. There was no significant difference between the three groups, with 5-year ESRF probability of 34, 34 and 35% for types I, II and III, respectively. Error bars depict the s.e.m.

Table 3 | Multivariate Cox regression analysis of factors potentially associated with ESRF

Variable	*P*-value	Hazard ratio (95% CI)
Age	0.62	1.02 (0.7–2.9)[a]
Gender	0.55	0.76 (0.4–1.7)[b]
MPGN type	0.89	1.21 (0.6–1.9)[c]
Creatinine at presentation	0.20	1.54 (0.7–2.8)[d]
Nephrotic syndrome	0.12	1.96 (0.8–6.2)[e]
Crescent on initial biopsy	0.002	10.2 (4.4–18.7)[f]
Degree of mesangial proliferation	0.03	1.72 (1.3–6.4)[g]
Degree of interstitial fibrosis	0.04	14.52 (1.2–27.8)[h]

[a]MPGN, membranoproliferative glomerulonephritis; CI, confidence interval <21 versus >21 years.
[b]Male versus female.
[c]Type II versus type I/III.
[d]>0.9 versus <0.9 mg/dl.
[e]Yes versus no.
[f]Yes versus no.
[g]>2 versus <2.
[h]>20 versus <20%.

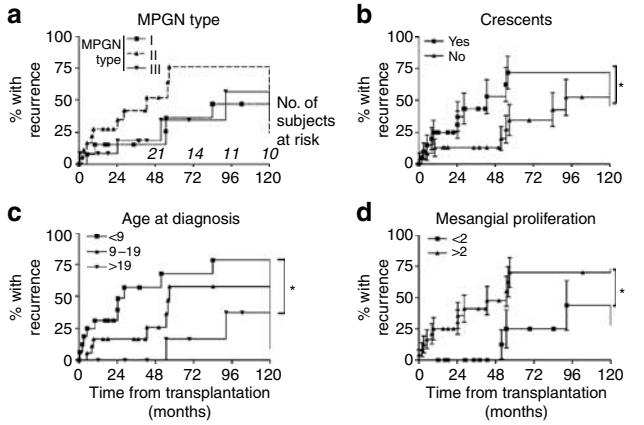

Figure 4 | Kaplan–Meier survival curves comparing the likelihood of recurrence in a renal transplant according to the following. (**a**) MPGN type. There was a trend towards a higher probability of recurrence in MPGN II with 5-year probability of recurrence 36, 76 and 34% for types I (■), II (▲) and III (▼), respectively ($P=0.1$). (**b**) The presence of cellular crescents on the initial biopsy. The probability of recurrence was higher in those with crescents (■, 5-year recurrence probability 72%) than in those without (▲, 5-year recurrence probability 35%, $P<0.05$). (**c**) Age tertile. Younger patients had a higher probability of recurrence: 69, 56 and 15% 5-year recurrence probability in those <9 (■), 9–19 (▲) and >19 years (▼), respectively ($P<0.05$). (**d**) The degree of mesangial proliferation on the initial biopsy. The probability of recurrence was higher in those with a mesangial proliferation score of 3–4 (▲) compared to those with a score <2 (▲, *$P<0.05$). Error bars depict the s.e.m.

Table 4 | Univariate analysis of factors potentially associated with recurrence of MPGN in the renal allograft

	Recurrence	No recurrence	*P*-value
MPGN type (n, %)			
I	6 (46)	7 (54)	0.1
II	11 (61)	7 (39)	
III	4 (33)	8 (67)	
Age (years) (mean, range)	14.2 (6–29)	22.9 (5–66)	0.02
Gender (n, %)			
Male	15 (50)	15 (50)	0.2
Female	6 (46)	7 (54)	
Nephrotic-range proteinuria at presentation (n, %)			
Yes	16 (48)	17 (52)	0.51
No	2 (40)	3 (60)	
Complement at presentation (n, %)			
Low	7 (47)	8 (53)	0.24
Normal	10 (55)	8 (45)	
Crescents at presentation (%) (mean, s.d.)	19.9 (20.9)	8.2 (15.3)	0.03[a]
Mesangial proliferation (mean, s.d.)	3.0 (0.9)	2.4 (0.7)	0.02

MPGN, membranoproliferative glomerulonephritis;
The variables are compared with Kaplan–Meier life table analysis using the log-rank test.
[a]Comparing those with crescents on initial biopsy with those with no crescents.

with recurrence and there was a trend towards an increased risk of recurrence in type II MPGN ($P=0.1$) (Figure 4, Table 4).

Multivariate analysis. As many of the factors described above are inter-related, we performed multivariate Cox regression analysis (Figure 5, Table 5). When variables indicative of glomerulonephritis severity (crescent formation, mesangial proliferation) were built into this model, the trend towards recurrence seen with MPGN type II was no longer present. Using this model, younger age at initial diagnosis ($P<0.05$) and the presence of crescents on the original biopsy ($P<0.005$) were independently associated with recurrence on multivariate analysis. All of the increase in recurrence seen in type II was statistically accounted for by the fact that these patients had more severe glomerulonephritis, as manifested by mesangial proliferation and crescent formation. The increase in recurrence risk in younger patients was not accounted for by the fact that there was a shorter interval between ESRF occurrence and transplantation. In fact, younger patients had to wait slightly longer for their transplant (median time from ESRF to transplant: 15 versus 18 months in those >16 and <16 years, respectively).

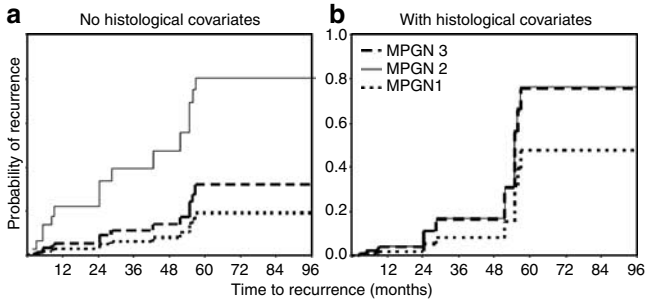

Figure 5 | Cox regression multivariate analysis of variables predicting recurrence of MPGN post transplantation, plotted at the mean of the covariates. (**a**) The covariates included were age, gender, MPGN type and the presence of nephrotic syndrome at first diagnosis. (**b**) To these were added histological variables (crescent fraction, degree of mesangial proliferation and interstitial fibrosis on the initial biopsy). (**a**) When histological variables are excluded from the analysis, there appears to be a trend towards increased recurrence risk with type II MPGN. (**b**) However, when the histological variables are taken into account, that is, controlling for mesangial proliferation and crescent formation, the association between MPGN type II and recurrence risk completely disappears (the curves for type I and III MPGN are superimposed).

DISCUSSION

In this large cohort of patients with primary idiopathic MPGN with prolonged follow-up, we have applied detailed statistical analysis in an attempt to identify those factors that are predictive of progressive renal failure and recurrence of the disease in the renal allograft. Our data suggest that it is the severity of acute glomerular injury on the initial biopsy (most notably the degree of mesangial proliferation and the presence of cellular crescents) that predicts risk of ESRF, not MPGN type *per se*. Those with MPGN type II appeared to do worse overall and this was because they had more severe glomerulonephritis.

Table 5 | Multivariate Cox regression analysis of factors potentially associated with recurrence in the renal allograft

Variable	*P*-value	Hazard ratio (95% CI)
Age	0.04	3.71 (1.02–7.7)[a]
Gender	0.13	1.99 (0.7–5.0)[b]
MPGN type	0.78	1.61 (0.5–4.8)[c]
Nephrotic at presentation	0.42	1.52 (0.4–5.1)[d]
Crescent on initial biopsy	0.005	6.88 (2.5–12.9)[e]
Degree of mesangial proliferation	0.65	0.95 (0.6–1.4)[f]

[a]MPGN, membranoproliferative glomerulonephritis; CI, Confidence interval <21 versus >21.
[b]Male versus female.
[c]Type II versus type I/III.
[d]Yes versus no.
[e]Yes versus no.
[f]<2 versus >2.

We have also identified a group with excellent (88% after 10 years) long-term renal survival (those with no cellular crescents, $<20\%$ interstitial fibrosis and $\leqslant +2$ mesangial proliferation), and a group with very poor (8% after 10 years) long-term renal survival (nephrotic patients with at least one crescent). Among the clinical variables tested, only nephrotic-range proteinuria at presentation predicted an increased risk of ESRF on multivariate analysis.

Idiopathic MPGN appears to be an uncommon disease in Ireland, diagnosed in just 1.8% of all native renal biopsies and accounting for 3.7% of all primary glomerulonephritis. Our study is representative of MPGN in the entire Republic of Ireland as, during the time period under study, most biopsies performed in the country were analysed at Beaumont Hospital. The majority of our patients presented with proteinuria in the nephrotic range associated with hypocomplementaemia. Overall, renal prognosis was poor, with half of our patients reaching ESRF in a little over 8 years. The absence of any cohort effect by decade of diagnosis suggests that we have made little progress in the treatment of this disease in the last 30 years.

With regard to risk of recurrent disease following renal transplantation, this appears to be unrelated to MPGN type. Indeed, on multivariate analysis, the only factors predictive of recurrence risk were younger age at initial diagnosis (69% recurrence risk at 5 years if aged <9 years compared with 0% if aged >19 years; $P<0.05$) and the presence of cellular crescents on the initial biopsy (72% recurrence risk at 5 years in those with crescents compared to 35% risk in those without; $P<0.05$). Of note, we were unable to account for factors such as possible inherited deficiencies of the complement cascade, which may have an important impact on recurrence risk. In instances where a clear family history of MPGN was present,[8,9] the case was not included in our study. Therefore, our findings do not necessarily apply to this group of patients.

On review of the literature in this field, our reported incidence of MPGN is commensurate with that reported elsewhere in the developed world.[1–3] Unusually, although in many parts of the world MPGN is now considered to be HCV associated in most cases,[5,6,11–14] this does not appear to pertain in Ireland. We have detected just one case of HCV-associated MPGN since introduction of routine testing for hepatitis C in Ireland in 1991. Furthermore, no case of hepatitis C has yet come to light among the patients with MPGN described in this report, and retrospective testing of available stored sera has not yielded any cases of previously undiagnosed hepatitis C. It may be that HCV-associated MPGN, while common in the USA and Japan, may not be as prevalent in Europe, and Ireland is certainly not unique in respect of this lack of association.[15–17]

The impact of MPGN type on renal survival is a point of particular interest given the widely held perception that type II disease is generally associated with a worse prognosis[18,19] and carries a significantly higher risk of recurrence following renal transplantation.[7,20–23] In fact, the evidence base for this assertion is relatively poor. Any apparent association between type II MPGN and poorer renal survival is likely to be illusory, merely reflecting the fact that type II disease is more likely to be associated with more aggressive initial histological changes (see Figure 1). This illustrates the pitfalls of analysing predictive variables in isolation from each other. One previous study (published in Russian)[24] has adopted a multivariate approach, although no attempt was made to analyse the interaction between MPGN subtype and histological variables, as in our case. Our findings challenge the dogma that there is something different about MPGN type II that renders it a more aggressive disease with a particular propensity to recur in the renal allograft.

The strengths of our study are its comparatively large sample size, long duration of follow-up and the multivariate approach to analysing factors (both clinical and histological) that may predict outcome. The inclusion of both adult and paediatric subjects and the exclusion of cases of MPGN secondary to HCV infection also strengthen the study. The main limitations are its retrospective nature and the limited availability of data regarding treatment (a potential confounding variable).

In conclusion, it is the severity of initial glomerular injury, rather than the MPGN type, that determines renal survival. When advising individual patients on what the future holds, we should look first to the initial renal histology for guidance rather than considering the MPGN type. In the context of transplantation, a diagnosis of type II MPGN should not of itself be considered a contraindication (even in the live-related setting), but rather one should review the details of the initial histology and take cognisance of the age at first diagnosis. The corollary also holds true, in that we should exercise caution in those patients with type I or III disease who presented at a younger age with a crescentic glomerulonephritis.

SUBJECTS AND METHODS

Study population

We performed our study at Beaumont Hospital, Dublin, the largest tertiary referral centre for nephrology in the Republic

of Ireland and the national centre for renal transplantation. The majority (80–85%) of renal biopsies performed in Ireland (native and transplant, adult, and paediatric) are reported by the Renal Pathology service at Beaumont.[25] It is therefore well placed to provide a representative picture of the pattern of MPGN disease in Ireland as a whole. We analysed each of the subtypes separately to determine differences in their clinical features, prognosis and rate of recurrence following renal transplantation.

Beaumont Hospital provides a diagnostic renal histopathology service to a population of approximately three million people. Using the laboratory database of Beaumont's renal pathology service, we attempted to identify all instances of MPGN demonstrated on native renal biopsy spanning the 23-year period from 1972 to 1995. Clinical data were drawn from patient medical records and from the tissue-typing database. The date on which the initial renal biopsy was performed was assigned as the date of diagnosis. All cases were followed until death or 1/4/2004 to ensure long-term follow-up. During this time, 2886 native renal biopsies were analysed, of which 1372 (47.4%) showed evidence of glomerulonephritis. Of those with glomerulonephritis, 240 (17.5%) demonstrated an immune deposition disease with a membranoproliferative pattern of injury.

We excluded from our analysis all patients with MPGN secondary to other identifiable conditions. Diagnoses in this group included systemic lupus erythematosus, hepatitis B/C, cryoglobulinaemia, and chronic infection (for example, infective endocarditis or infected ventriculo-atrial shunt). Specifically, after 1991, all sera were tested for HCV antibodies and only one instance of HCV-associated MPGN was identified (and excluded). Other causes of glomerular injury with a potential membranoproliferative pattern, such as chronic thrombotic microangiopathy and fibrillary glomerulonephritis, were also excluded.

A total of 83 patients remained (6.1%), who were designated as having idiopathic MPGN; of these, 13 were lost to follow-up (three type I, five type II, and five type III), leaving 70 cases, which form the basis of this report. The mean age at time of biopsy was 24.9 years (range 3–76) and 41 (59%) were male. In order to exclude a cohort effect, we defined three cohorts: before 1979 ($n=20$), 1979–1989 ($n=30$) and after 1989 ($n=20$). Treatment modalities were subdivided into the following groups: (1) no treatment ($n=9$), (2) steroid treatment (with or without additional antihypertensive therapy $n=20$) and (3) antihypertensive therapy alone ($n=30$). Accurate data on treatment were not available in 11 patients. Patients were assessed until the time of last follow-up or death. The patients were followed for a total of 968 patient-years (mean follow-up 13.8 years, range 1.2–30.3).

Histopathology

We subdivided the cases by histological classification into types I–III according to the biopsy report with blinded review of histology, immunofluorescence and electron microscopy performed in all cases. We quantified the percentage of cellular glomerular crescents (defined as occupying $>10\%$ of the glomerulus), sclerosed glomeruli, and amount of interstitium fibrosed on the renal biopsy. In addition, we scored the degree of mesangial proliferation from 0 to 4. Clinical follow-up data were collected on serum creatinine at presentation ($n=68$), presence or absence of nephrotic-range proteinuria (>3 g/24 h, $n=67$) and complement C3 level at presentation ('normal' or 'low', $n=55$). The need for long-term renal replacement therapy and the clinical course following renal transplantation, including recurrence of primary disease, were recorded. All cases of recurrence of MPGN were diagnosed by histological immunofluorescent and ultrastructural examination of a transplant renal biopsy.

Literature review

To place our study in the proper context, we conducted a comprehensive literature review using Medline (1966–2005) and Embase (1983–2005). The following search terms were used: MPGN; hypocomplementaemic glomerulonephritis; lobular glomerulonephritis; membrane proliferative glomerulonephritis; membranoproliferative nephritis; membranous proliferative glomerulonephritis; mesangiocapillary glomerulonephritis; mesangioproliferative glomerulonephritis; rapidly progressive glomerulonephritis. A total of 4415 Medline and Embase entries were reviewed. We examined 81 studies (excluding case reports) reporting outcome in idiopathic MPGN, the majority of which were retrospective and uncontrolled. Details of a selection of frequently cited key studies are listed in Table 6 to allow comparison with our own data.

Statistical analysis

Skewed data sets were expressed as the median and interquartile range and analysed using non-parametric tests. Normally distributed data sets were expressed as mean and standard error of the mean. The probability of developing ESRF over time and recurrence of MPGN in a renal transplant were analysed with Kaplan–Meier survival plots using SPSS 9.0 software. Univariate analysis of factors potentially associated with the development of ESRF or recurrence in the renal allograft were compared with the log-rank test, with censoring in the event of patient death or passing the date 1/4/2004. Continuous variables (for example, age, creatinine at presentation, degree of interstitial fibrosis) were divided into tertiles for this purpose. Those factors associated with ESRF or recurrence on univariate analysis at a significance level of $P<0.2$ (in addition to age and gender) were analysed using a multivariate Cox regression proportional hazards model. The assumption of proportionality was tested for each variable. A P-value of $\leqslant 0.05$ was considered to indicate statistical significance and all tests were two-tailed.

Table 6 | Overview of some of the principal studies evaluating outcome in idiopathic MPGN

Reference	Study design	N	Mean follow-up (years)	Patient characteristics	Renal survival	Adverse prognostic features	Comments
This study	Retrospective cohort analysis	70	13.8	Adult and paediatric	Median time to ESRF 8.3–20 years – 30%	Crescents on initial biopsy Mesangial proliferation Nephrotic-range proteinuria	MPGN type *not* predictive of risk of ESRF or recurrence post transplantation
Cansick *et al.*[26]	Retrospective cohort analysis	53	3.5	Paediatric	Type I/III – 10.9 years Type II – 9.9 years	Chronic damage on initial biopsy Nephrotic syndrome Subnormal eGFR at 1 year	Outcome not better in children who received immunosuppression, MPGN type not predictive of ESRF
Schwertz *et al.*[18]	Multicentre observational study	50	11.4	Paediatric	Type I – 15.3 years Type II – 8.7 years Type III – 15.9 years	Nephrotic syndrome	More ESRF with type II Hypocomplementaemia did not predict progression
Pedersen[27]	Observational study	37	2.7	Adult and paediatric	5-year survival – 35% 10-year survival – 16%	Older age Hypertension	
Iitaka *et al.*[28]	Retrospective cohort analysis	41	8.75	Paediatric Majority diagnosed by childhood urine screening	97.60%	Prognostic factors not analysed	Better outcome may reflect: Crescents in only 5% Early diagnosis Few type II cases
Tarshish *et al.*[29]	Randomised controlled trial	80	5.25	Paediatric glomerular filtration rate > 70 All had nephrotic syndrome	10-year survival: Prednisone – 61% Lactose – 12%	Mesangial hypercellularity (inverse correlation)	
McEnery[30]	Observational study	76	10.6	Paediatric	10-year survival – 82% 20-year survival – 56%	Prognostic factors not analysed	71/76 treated with prednisone
Schmitt *et al.*[31]	Retrospective cohort analysis	220	5	Adult and paediatric Type I only	5-year survival – 51% 10-year survival – 36%	Hypertension Glomerular crescents Interstitial fibrosis	Mainly adults (< 5% below 15 years)
Orlowski *et al.*[32]	Observational study	50	10	Adult	5-year survival – 90% 10-year survival – 82% 15-year survival – 77%	Hypertension	Majority treated with Pred/Aza/chlorambucil
Swainson *et al.*[33]	Observational study	40	5–22	Adult and paediatric (12%)	5-year survival – 58% 10-year survival – 48%	Hypocomplementaemia Glomerular crescents Impaired renal function at presentation	Nephrotic syndrome associated with reduced patient survival No difference in outcome for type I versus II
Cameron *et al.*[19]	Observational study	104	8	Adult and paediatric	Type I – 62% Type II – 51%	Glomerular sclerosis Glomerular crescents Nephrotic syndrome Type II disease	Nephrotic syndrome predictive of progression in type I only
Habib *et al.*[34]	Retrospective cohort analysis	105	5.75	Paediatric	Type I – 66% Type II – 45%	Glomerular crescents Type II disease Nephrotic syndrome Macroscopic haematuria Impaired renal function at presentation	MPGN type assigned by light microscopic examination (electron microscopy in 11% only) Prognosis in type I + II similar if patients with crescents were excluded

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